DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-16-09 has been entered.

Claims 6, 7, 9, 11, 12, 21, 23-26, 29, 36-39 and 41 have been canceled. Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 remain pending.

Applicant's arguments filed 11-16-09 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The title of the invention will have to be changed to more closely reflect the fact that the claims are limited to a transgenic mouse or rat.

Claim Rejections - 35 USC § 101

The rejection of claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. 101 because the claimed invention lacks patentable utility has been withdrawn because agonists and antagonists of C5aR were known in the art as being used for therapy (pg 2, lines 9-21). One such known antagonist to C5aR known to treat disease

was 3D53 (Monk of record, 2007; pg 436, paragraph bridging col. 1-2; col. 2, 1st full paragraph). Monk (2007) summarized treatment using 3D53 on pg 437 (Table 2), many of which were known prior to 12-24-03 (see "References" column of Table 2, which was many references published in 2003 or before). In addition, pg 62, lines 20-35, discuss a method of screening drugs using homozygous human C5aR knockin mice.

Claim Rejections - 35 USC § 112

Enablement

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

C5aR

C5a binds C5a receptor (C5aR) (pg 1, line 28).

Morgan (WO 95/00164) taught human C5a is one of the best described and most potent proinflammatory mediators derived from the complement system. Morgan states C5a possess multiple biologic activities that relate to host defense and may play a role in inflammatory disease processes.

Since the time of filing, Lee (Nature Biotech., Oct. 2006, Vol. 24, No. 10, pg 1279-1284) taught C5a binding C5aR facilitates leukocyte chemotaxis and release of inflammatory mediators (abstract), which is not disclosed in the instant specification. In fact in 2007, Monk (British J. Pharm., 2007, Vol. 152, pg 429-448) taught the function of

C5aR was previously misunderstood and the understanding of the physiology of C5a improved by using knockout and knockin mice (pg 429, abstract).

Claims 1-5, 8, 10, 12, 14-20, 22, 27, 28, 30-35 and 40 currently encompass making any knockin mouse or rat; however, the specification teaches the invention requires two major elements: an ES cell line and a targeting construct (pg 50, lines 29-31). The specification and the art at the time of filing do not teach how to make knockin rats or rat ES cells. The specification does not teach a targeting construct that would target the rat C5aR gene. Without such guidance, it would have required those of skill undue experimentation to determine how to make transgenic knockin rats or how to make rat ES cells used to make such rats. Accordingly, the claims should be limited to knockin mice.

The claims also encompass using a heterozygous or homozygous transgenic knockin mouse. However, the specification does not teach how to use a heterozygous mouse expressing both human AND mouse C5aR. The specification and the art at the time of filing do not teach how to use such a mouse to screen drugs. The specification is limited to using homozygous C5aR mice to screen compounds for anti-inflammatory properties. Thus, it would have required those of skill in the art at the time of filing undue experimentation to determine how to use heterozygous C5aR mice to screen compounds, and the claims should be limited to homozygous C5aR mice.

The claims encompass mice expressing human C5aR while still expressing their endogenous C5aR gene. The specification and the art at the time of filing do not teach how to use a mouse expressing both human C5aR while still expressing their

endogenous C5aR gene. The specification is limited to a transgenic mouse whose genome comprises a homozygous disruption in a mouse C5a receptor gene, and whose genome is homozygous for a nucleic acid sequence encoding human C5aR. Thus, it would have required those of skill in the art at the time of filing undue experimentation to determine how to use heterozygous C5aR mice to screen compounds, and the claims should be limited to homozygous C5aR mice.

Claim 15 is drawn to making a transgenic mouse using a targeting vector. Claim 1 is drawn to a transgenic mouse comprising a polynucleotide encoding a human or humanized C5aR. The specification fails to adequately teach those of skill to make the knockin mouse described in Example 1. Accordingly, the specification fails to adequately teach how to perform the method of claim 15 or to make the mouse of claim 1. Pg 51, lines 9-16, discusses Fig. 1, which describes the targeting construct used to make the transgenic mice in the Examples. However, the structure of the targeting construct is not readily apparent from Fig. 1. In particular, the region of "mouse-human fusion" is unclear and does not teach what area of the mouse C5aR has been replaced with human sequences or what promoter is driving the human C5aR sequences. Such information is essential to make applicants invention, and without such guidance, it would have required those of skill in the art at the time of filing undue experimentation to determine how to use heterozygous C5aR mice to screen compounds, and the claims should be limited to homozygous C5aR mice. Applicants' arguments regarding obviousness include mention of unexpected results that human C5aR would bind mouse C5a. Assuming that is true, this goes towards unpredictability of the invention,

and applicants have failed to enable those of skill in the art by teaching the essential human C5aR sequences used to replace endogenous mouse C5aR sequences and the structure of the targeting vector. It is also noted that the targeting vector requires a cre-lox system which is not in the claims. If cre-lox elements are essential in the targeting vector to make the mouse, then the structure of the targeting vector must be included in the mouse claimed and include the cre-lox elements that are essential to make the mouse.

Claim 28 is drawn to evaluating a compound by administering the compound to the mouse of claim 1 (or isolated tissues or cells obtained therefrom) and examining a pharmacokinetic/pharmacodynamic effect of the compound. However, the specification fails to enable those of skill to determine how to use the mouse of claim 1 to screen drugs. The specification teaches agonists and antagonists of C5aR were known in the art as being used for therapy (pg 2, lines 9-21). One such known antagonist to C5aR known to treat disease was 3D53, which was described in 1999 by Wong (IDrugs, 1999, Vol. 2, pg 686-693) (see Monk of record, 2007; pg 436, paragraph bridging col. 1-2; col. 2, 1st full paragraph). Monk (2007) summarized treatments of disease using 3D53 on pg 437 (Table 2), many of which were known prior to 12-24-03 (see "References" column of Table 2, which was many references published in 2003 or before).

The specification teaches using the knockin mice to screen anti-inflammatory compounds (pg 7, lines 23-30; pg 59, line 23). The knockin mice were subjected to sera from a K/BxN model of rheumatoid arthritis; K/BxN mice express a transgene encoded T cell receptor (TCR) reactive to a self-peptide derived from the ubiquitously

expressed glycolytic enzyme GPI, wherein the mice spontaneously develop arthritis (pg 59, lines 26-36). Sera from arthritic K/BxN mice was injected intraperitoneally into H5Rf/H5Rf knockin mice (pg 61, lines 16-21). The mice develop signs of inflammation indicating the human C5aR is expressed and the receptor is processed correctly to the G-protein signaling system (pg 61, lines 24-26; pg 62, lines 4-9). The specification states:

"The human C5aR knock-in mice were developed as a useful tool to screen anti-human C5aR compounds for anti-inflammatory activity. To test the utility of the mice we administered both homozygous hC5aR and wild-type (control) mice an antibody specific for human C5aR (it does not bind to mouse C5aR) or a control antibody (same isotype but irrelevant specificity) in the K/BxN model and determined the effect of the antibody on inflammatory disease progression. The antibody was injected i.p. twice (200 ug per dose), one day before and one day following the first K/BxN serum injection. Mice were monitored as described above." (pg 62, lines 20-27)

Overall, it is unclear how the "homozygous hC5aR and wild-type (control) mice" are "in the K/BxN model" as described by applicants; the specification does not clearly set forth that knockin mice and wild-type mice were both given K/BxN sera. Second, it was predetermined that the anti-human C5aR antibody targeted hC5aR and not mouse C5aR, so the controls required to identify compounds that specifically target hC5aR using the mice claimed are not described by applicants. Pg 62, lines 20-35, discuss a method of screening drugs using homozygous human C5aR knockin mice without teaching the specific steps required to do so. Applicants have left those skilled in the art with no information how to use the non-human mammals claimed to identify compounds that target human C5aR. Finally, merely observing whether a compound known to specifically target human C5aR decreases inflammation in a knockin mouse (given

K/BxN sera?) as compared to a control is not an enabled use in and of itself because the compound was already known to treat disease. Therefore, using the knockin to screen anti-inflammatory compounds already known to target human C5aR is not an enabled use. As such, applicants have merely provided a starting point for further research and not provided an end point of a research effort in determining how to identify compounds of interest using the knockin claimed.

Applicants argue the percent identity of mouse, rat and human C5aR which has nothing to do with the rejection at hand. The specification and the art at the time of filing do not teach how to make knockin rats or rat ES cells.

Applicants argue those of skill could readily make a knockin rat based on the information provided in the specification. Applicants' argument is not persuasive because it is unfounded.

Claim Rejections - 35 USC § 103

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (Thrombosis and Haemostasis, 1999, Vol. 82, No. 2, pg 865-869), Roebroek (Methods in Molecular Biology, 2003, Vol. 209, 187-200), Homanics (2002, Methods in Alcohol related neuroscience research, Editor, Liu, Yuan, pg 31-61), Lester (Current Opin. Drug Discovery and Development, 2003, Vol. 6, No. 5, pg 633-639), Champtiaux (Current Drug Targets-CNS & Neurological Disorders, 2002, Vol. 1, pg 319-330), Girardi (J. Clin. Invest., Dec. 2003, Vol. 112, No. 11, pg 1644-1654) in view of Burmer (WO 02/61087-A2) for reasons of record.

Sato taught a knock-in mouse had an endogenous gene replaced with an exogenous gene or a mutant form of the endogenous gene (pg 866, col. 1, Gene Knock-in). Roebroek taught various strategies for making knockin mice and provided numerous references prior to applicants effective filing date that describe disrupting an endogenous mouse gene and replacing it with the human homologous cDNA (pg 188, 2.2; pg 190-191, 3.1). One example of a receptor mouse known at the time of filing was Homanics who taught disrupting a mouse receptor gene and replaced with homologous human receptor cDNA. Other examples of receptor knockin mice are described by Lester and Champtiaux. Cells were isolated from the mice, and compounds were administered to the mice for pharmacokinetic evaluation. Sato, Roebroek, Homanics, Lester, Champtiaux did not disrupt the mouse C5aR gene and replace it with human C5aR cDNA.

However, knocking out the mouse C5aR gene in a mouse was known in the art at the time of filing as described by Girardi. Furthermore, human C5aR cDNA was known in the art at the time of filing as described by Burmer (SEQ ID NO: 79).

Thus it would have been obvious to those of ordinary skill in the art at the time the invention was made to make a humanized receptor knockin mouse as was well known in the art at the time of filing using the human C5aR cDNA of Burmer. Those of ordinary skill in the art at the time the invention was made would have been motivated to replace the mouse C5aR gene with human C5aR cDNA to test the functional redundancy of the gene, i.e. to test whether or not the exogenous gene can replace the function of the endogenous gene.

Applicants argue those of skill would not expect the human C5aR in the transgenic claimed to be activated by mouse C5a or that it would function. Applicants point to Exhibit 3 which shows the homology of the extracellular domain of mouse, rat and human C5aR. Applicants' argument is not persuasive. Cain (Biochemical Pharm., 2001, Vol. 61, No. 12, pg 1571-1579) taught human, mouse and rat C5aR shared significant homology (pg 1574, Fig. 1) and discuss two peptides that inhibit C5a binding and function at human and rat C5aRs (pg 1572, col. 1, lines 10-13). Despite the homology of the extracellular domain of mouse, rat and human C5aR, those of ordinary skill would have a reasonable expectation of mouse C5a binding human C5aR because Cain taught a peptide that inhibited rat C5a binding to rat C5aR would also function at human C5aR.

Applicants argue those of skill would not have had a reasonable expectation of success in making a knockin C5aR mouse using the combined teachings of Sato, Roebroek, Homanics, Lester, Champtiaux, Girardi and Burmer.

Applicants argue the combined teachings of Sato, Roebroek, Homanics, Lester, Champtiaux, Girardi and Burmer had unexpected results because human C5aR would not be expected to function in a mouse and bind mouse C5a. Applicants argue the mouse and human C5a and C5aR share only about 70% identity. Applicants point to Exhibit 2 which shows the percent identity of mouse and human C5a and Exhibit 3 which shows the percent identity of the extracellular domains of mouse and human C5aR. Applicants point to Woodruff (Inflammation, 2001, Vol. 25, No. 3, pg 171-177) as support for the unpredictability of cross species functioning as ligands. Applicants'

arguments are not persuasive. Knockin mice expressing human or humanized receptors having less than 100% were known in the art to function at the time of filing. Woodruff merely teaches that different species of ligands (mouse vs. rat vs. human) bind with different affinities; Woodruff does support applicants' argument that it was unpredictable that the mouse C5a would fail to bind to human C5aR and function to some degree. Furthermore, Sato, Roebroek, Lester and Champtiaux taught knockin mice that expressed humanized receptors that shared less than 100% homology with the mouse equivalent receptor. In addition, knockin mice having a humanized receptor were known in the art to bind the mouse ligand as exemplified by Drago (Cellular and molecular life sciences, July 2003, Vol. 60, pg 1267-1280), Gu (Developmental Cell, July 2003, Vol. 5, pg 45-57), Belmont (WO 2002/059263) and Kane (WO 2003/027252). Finally, the claims encompass mice having a point mutation in the mouse receptor that is found in the human receptor (a humanized receptor as claimed); the claims are not limited to a mouse expressing the entire human C5aR in the absence of the mouse C5aR. Thus, those of ordinary skill in the art at the time of filing would have had a reasonable expectation of obtaining a mouse expressing a human C5aR or humanized C5aR that bound mouse C5a that effects signaling as claimed.

Applicants mention the art being unpredictable around Dec. 2003 but fail to provide any references from Dec. 2003. Clarification is required.

Applicants' discussion of human C4a cross-interacting with guinea pig C3aR but not human C3aR is noted is not persuasive because cross-binding of C4a to C3aR does not correlate to C5a binding C5aR.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Woodruff (Arthritis and Rheumatism, Sept. 2002, Vol. 46, No. 9, pg 2476-2485).

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

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